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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,780	07/27/2001	Yi Li	883933.0066	9604

21874 7590 06/01/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
HELMER, GEORGIA L	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,780	LI ET AL.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-48* is/are pending in the application.

4a) Of the above claim(s) *38-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence Compliance forms*.

DETAILED ACTION - RCE

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 January 2004 has been entered.

Status of the Claims

2. Applicant has cancelled claims 1-24, and added claims 25-48.

3. Newly submitted claims 25-48 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly added claims are directed to the following distinct inventions:

IV. Claims 25-37, drawn to a method of making transgenic plants, classified in class 800, subclass 278, for example.

V. Claims 38-45, drawn to a gene cassette, classified in class 536, subclass 23.1, for example.

VI. Claims 46-48, drawn to a gene cassette comprising a fusion gene that encodes Cre and R, classified 23.4.

For each of the inventions of Groups IV-VI, restriction to the following is also required under 35 USC 121. Therefore, Applicant is required to elect one of inventions IV-VI, one of inventions (a) – (l), and one of *(i)-(viii)*.

The nucleic acid expresses a protein:

(a) FLP.

(b) Cre.

(c) R.

(d) Gin.

(e) PIV.

(f) FimB

(g) C31.

(h) KW.

(i) SSV.

(j) IS1110IS492

(k) ParA.

(l) TnpX.

The organ-, developmental-or inducible-promoter is

(i) AG.

(ii) AGL5.

(iii) Bcp1.

(iv) LAT52.

(v) PLENA.

(vi) SIM.

(vii) avrRp2.

(viii) alc.

4. Inventions IV and V/VI are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product. The DNA gene cassettes can be as hybridization probes. Inventions V and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions they have different modes of operation, different functions, or different effects. The group V products have different starting materials and different steps than the group VI products.

5. Inventions (a)-(l) and *(i)-(viii)* are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because many regulated promoters are known in the

art. The subcombination has separate utility such as a means for expressing antisense RNA.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and the literature and sequence searches required for each of the Groups are not required for another of the Groups, restriction for examination purposes as indicated is proper.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 38-48 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

8. Claims 25-48 are pending, and claims 25-37, drawn to Group IV, where the recombinase protein is FLP and the inducible promoter is Bcp1 are examined in the instant action.

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections

10. The claims are objected to because the lines are crowded too closely together, making reading and entry of amendments difficult. Substitute claims with lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52(b).

In claim 25 line 10, "sequence" is misspelled.

Sequence Listing

11. Applicant is not in compliance with the sequence requirements as set forth in 37 CFR 1.82-1.85 (see claim 48, for example). Attached are documenting papers setting forth the required response.

Claim Rejections - 35 USC § 112, second paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 25,

- "gene" is unclear because a "gene" implies a DNA sequence that exists in nature and includes coding and noncoding regions, as well as all regulatory sequences associated with expression. Since this

does not appear to be Applicant's intention, the language "a DNA of interest" is suggested. Or Applicant may recite the various components of the "gene" desired.

- line 5, "a first DNA recombinase recognition sequence" is indefinite because "first" can refer to the recombinase or the recognitions sequence. Suggested language is "a recognition site for a first recombinase". This is of particular importance in this case which includes multiple recombinases and multiple recognition sites, and combinations thereof. "DNA excision sequences" is unclear; how do excision sequences differ from non-excision sequences? Claims 26 and 27 have a similar problem, with "two different recombinase recognition sequences".
- line 8, "stimulation" lacks antecedent basis. Further, it is unclear what activities are encompassed by "stimulation".
- line 9, it is unclear what is "causing excision"–the promoter or recombinase.

Claim 25 is an incomplete method claims, because it does not results in the "reversible introduction of heterologous DNA".

In claims 25, 34 and 25, it is unclear what to do if the trait of interest is controlled by more than one DNA sequence, or it is not know what DNA sequence confers a particular trait of interest. Suggested language is changing "trait" to "protein".

In claims 30, 31 and 36, "the recombinase coding DNA" lacks antecedent basis.

In claim 35, only disease resistance and sterility are traits. The other items listed are not traits as they are not distinguishing characteristics. For example, while "compact appearance" may be a trait, "appearance" in general is not a trait.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 25-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejected subject matter is "FLP, Cre, R, Gin, PIV, FimB, C31, KW, SSV, IS1110IS492, TnpX, AG, AGL5, Bcp1, LAT52, PLENA, SIM, avrRp2, and alc". Applicant is invited to point out the page and line number in the specification where these terms can be found. Absent such support, Applicant is required to cancel the new matter in response to this Office Action.

15. Claims 25-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising introducing a gene, said heterologous DNA flanked 3' by a Lox/FRT molecular hybrid recombinase recognition sequence, and flanked 5' by DNA encoding FLP recombinase operable linked to a Bcp promoter that is downstream of a second Lox/FRT molecular hybrid recombinase recognition sequence, said Lox/FRT sequences being in direction repeat orientation, does not reasonably provide enablement for the broad scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)):

Nature of the invention. Applicant's claims are drawn to a method for reversible introduction of heterologous DNA in a plant genome comprising introducing a gene cassette into a plant, said cassette comprising a heterologous DNA conferring a trait of interest, said heterologous DNA flanked 3' by at least a first DNA recombinase recognition sequence and flanked 5' by at least one DNA encoding a first recombinase operably linked to a an organ-specific, developmental stage-specific or inducible promoter that is downstream from a second recombinase recognition sequence wherein stimulation of the promoter induces expression of the recombinase causing excision of DNA located between the recombinase recognition sequences, where the recombinases are

FLP or Cre, where the first recombinase recognition sequence is FRT or LoxP, and where the cassette comprised a marker gene between the recombinase recognition sequences. Claims are also drawn to heterologous DNA encodes a phenotypic plant trait, where the recompose is FLP, Cre, R, Gin, PIV, FimB, C31, KW, SSV, IS1110IS492, TnpX, and where the regulated promoter is AG, AGL5, Bcp1, LAT52, PLENA, SIM, avrRp2, and alc.

The claimed methods use recombinase systems to modify gene expression.

State of the prior art and the predictability of the art: The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364; Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109; Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152). Inventor Li acknowledges (Attachment B, Manuscript, page 8, 1st line of 1st full ¶) the problems of low and variable excision frequencies. Excision

frequencies of Cre or FLP are generally low in higher plants (Ow, D. Plant Molecular biology, Vol 48, pages 183-200, 2002; and Hare et. al., Nature Biotechnology, Vol 20, pages 575-580, 2002). The claimed methods require use of recombinase-type systems to delete appropriately flanked DNA sequences.

Breadth of the claims. Claims are broadly drawn to all recombinases, all plants—including monocot and dicots, gymnosperms--, all traits and all marker genes. Recombinases and recombinase sites are encompassed broadly; Applicant describes site specific recombinases, but claims all recombinases.

Working examples. See the Declaration of Dr. Yi Li, below.

Guidance in the specification. The specification contains three prophetic examples: Prophetic Example 1 describes (p 32) a gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a vegetatively propagated plant. Prophetic Example 2 describes (p 33) a second gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a vegetatively propagated plant. And Prophetic Example 3 (p 35) describes a gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a sexually propagated plant.

Applicant describes a series of steps that one of skill in the art could take to try to produce various desired outcomes. These desired outcomes are all predicated on the ability of a recombinase gene being expressed and successfully excising a DNA specific sequence from a DNA sequence flanked by DNA recombinase excision sequences. If the DNA excision reactions do not function faithfully and at a very high frequency, none of the more complicated

steps of the multi-tiered cascade, will function as desired. Applicant gives no specific details of any DNA constructs, nor any results of use of the various generally described systems to function as desired. Various parameters that need to defined, such as: what DNA sequence do you put where, in what proximity to other DNA sequences, in what orientation with respect to transcription, in cis or trans configuration to one another, and how large a DNA sequence will function in the various pieces. Applicant offers no information on any of this, other than to list various pieces of DNA which might work in the various desired functions.

Amount of Experimentation necessary. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

In view of the breadth of the claims (to all recombinases, all plants, all traits and all marker genes), the lack of guidance in the specification, and the unpredictability in the recombinase art, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

The Declaration of Dr. Yi Li

16. The Declaration of Dr Yi Li has been thoroughly considered and found to be persuasive. The Declaration of Li states (¶ 3) that "I have demonstrated in several working examples that gene cassettes incorporated into plants can be 100% excised from the transgenic plant by employing the methods disclosed" in

the application. Li also says the "I have combined LoxP (34bp) and/or FRT (48bp) recognition sequences in direct orientation as flanking sites for a FLP and/or Cre recombinase gene engineered to express in pollinating plants when an operatively linked promoter is activated. The gene cassette, including a GUS reporter gene, was constructed using standard techniques details in the paper provided as Attachment A.... [A]nalyses showed that the reporter gene and the sequence between the recombinase excision sites were 100% deleted, leaving only a short nonfunctional DNA fragment not excised."

Dr Li documents (¶ 4) experiments done by him, using "LoxP/FRT", a molecular hybrid of recombinase recognition sequences of two different recombinase enzymes as flanking sites for a FLP recombinase coding sequence operatively linked to the Bcp1 pollen specific promoter. These experiments were preformed in R-1 transgenic tobacco plants resulting from sexual crosses of a plant bearing a ["Lox/FRT"-- 35S-Gus—Bgp-FLP—"Lox/FRT"] with a wild-type plant.

The Declaration of Li documents an invention, but fails to enable the claimed invention commensurate in scope with the claims.

Remarks

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0796. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

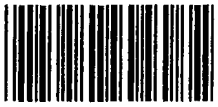
Georgia L. Helmer
Patent Examiner
Art Unit 1638
May 13, 2004

PHUONG T. BUI
PRIMARY EXAMINER

Sequence Count Sheet

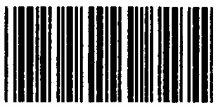
Application No: 09/916 780 Examiner: GHelmer

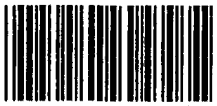
Date of Count: _____

_____  (*1055*)+ 1: CRF is unreadable; use CRF Diskette Problem Report.

_____  (*10551*)+2: CRF does not comply; use Notice to Comply.

X  (*10552*)+ 3: CRF required but none submitted; use Notice to Comply.

_____  (*1057*): Second or subsequent letter to applicant reporting bona fide; attempt to comply; use Notice to Comply and send copy of RSL.

_____  (*1058*): Second or subsequent letter to applicant reporting bona fide attempt to comply; use Notice to Comply and send copy of RSL.

Remarks: _____

Application No. 09/916,780

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.

COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DEA/FACE-1994

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/916,780			

EXAMINER	
DR. GEORGIA HELMER	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application
Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Any inquiry concerning this communication should be directed to

at telephone number (~~703) 308-4025~~ 571-272-0796

DR. GEORGIA HELMER

see claim 48
→ the 8 amino acid sequence